

Measurement of Parathyroid Hormone Level in Early Diagnosis of Hypocalcemia After Total Thyroidectomy

Total Tiroidektomi Sonrası Oluşan Hipokalseminin Erken Tanısında Paratiroid Hormon Seviyelerinin Ölçümü

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ABSTRACT

Aim: Hypoparathyroidism is a major complication of thyroid surgery. Inadvertent removal of the parathyroid glands or nutritional deterioration of the parathyroid glands are the most important mechanisms that explains the reduction of postoperative parathyroid functions. In this study, postoperative parathyroid hormone (PTH) level was analyzed in order to prevent hypocalcaemia and enable the patients to be discharged safely.

Patients and Methods: Preoperative calcium level, postoperative 20 minutes, 4 hours, 24 hours levels, 10 days and 6 months calcium level and 20 minutes, 4 hours and 24 hours PTH level and postoperative complications and histopathology results of the 85 patients who had total thyroidectomy were recorded. Patients were given calcium carbonate and/or calcitriol or they were discharged without any treatment depending on their PTH level on the postoperative 24 hours.

Results: In our study, PTH levels analyzed on the postoperative 20 minutes, 4 hours and 24 hours were found to be statistically significant ($p:0,0001$) to be able to detect hypocalcaemia in an early stage. However PTH level was found to be statistically more sensitive (%91.5) on the postoperative 20 minutes. In our study, postoperative calcium levels were not found to be significant in detecting hypocalcaemia in an early stage that may develop after total thyroidectomy.

Conclusion: We are in the opinion that with a PTH level analyzed on the 20th postoperative minute, patients can be discharged safely 24 hours after the surgery; furthermore, we also believe that in the presence of a higher level than 10 pg/ml PTH level we will not observe postoperative hypocalcaemia symptoms.

Key words: Total thyroidectomy, hypocalcemia, parathyroid hormone, hypoparathyroidemia.

ÖZ

Amaç: Hipoparatiroidizm, tiroid cerrahisinin önemli bir komplikasyonudur. Paratiroid bezlerinin istenmeden çıkarılması veya beslenmesinin bozulması postoperatif paratiroid fonksiyonlarının azalmasını açıklayan en önemli mekanizmalardır. Bu yazıda hastaların hipokalsemi gelişmemesi için güvenle taburcu edilebileceği postoperatif paratiroid hormon (PTH) değeri araştırıldı.

Hastalar ve Yöntemler: Total tiroidektomi yapılan 85 hastanın preoperatif kalsiyum değerleri, postoperatif 20. dakika, 4. saat, 24. saat, 10. gün ve 6. ay kalsiyum değerleriyle 20. dakika, 4. saat ve 24. saat PTH değerleri, ameliyat sonrası dönemde gelişen komplikasyonlar ve histopatoloji sonuçları kaydedildi. Hastalar postoperatif 24. saat PTH değerine göre kalsiyum karbonat ve/veya kalsitriol verilerek ya da hiçbir tedavi verilmeden taburcu edildiler.

Bulgular: Çalışmamızda postoperatif 20. dakika, 4. saat ve 24. saatte ölçülen PTH değerleri hipokalseminin erken dönemde saptanması açısından istatistiksel olarak anlamlı bulundu ($p:0,0001$). Fakat 20. dakika PTH değeri istatistiksel olarak daha duyarlı bulundu (%91.5). Total tiroidektomi sonrası gelişebilecek hipokalseminin erken dönemde tespitinde postoperatif kalsiyum değerleri çalışmamızda anlamlı bulunmamıştır.

Sonuç: Postoperatif 20. dakikada ölçülecek PTH değeri ile hastaların 24. saatte güvenle taburcu edilebileceğini ve 10 pg/ml'den büyük PTH değerleri varlığında postoperatif hipokalsemi semptomlarıyla karşılaşmayacağını düşünüyoruz.

Anahtar Kelimeler: Total tiroidektomi, hipokalsemi, paratiroid hormon, hipoparatiroid

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INTRODUCTION

Thyroidectomy, meaning partial or complete removal of thyroid tissue, is one of the most commonly performed surgical procedures among general surgery and endocrine surgery clinics. The surgical method selected for thyroid diseases requiring surgical treatment should help eliminate the disease and allow keeping the postoperative complications in a minimum level [1]. Parathyroid glands are sensitive structures that are easily affected by a trauma and during a thyroid surgery they may be damaged directly or indirectly [2]. Inadvertent removal or impaired feeding of the parathyroid glands are the most important mechanisms that explain the decrease in postoperative parathyroid function. Permanent hypoparathyroidism affects in a negative way the quality of patient's and the patient use lifelong medication.

In this research, we aimed to specify the patients under risk for symptomatic hypoparathyroidism and hypocalcaemia in an early stage, initiate early clinical treatment for these patients and discharge the patients not under risk and lower the length of their hospitalization by planning a prospective randomized work after total thyroidectomy.

PATIENTS AND METHODS

This study was carried out in the Department of General Surgery, Medical Faculty of Akdeniz University. This department has a section that works specifically in endocrine surgery. In this study 85 patients above the age of 18 without a kidney function disorder and did not have thyroid or parathyroid surgery before were prospectively recruitment between January 2011 and July 2011. These patients were operated for thyroidectomy caused by benign or malign thyroid diseases. Preoperative calcium levels, postoperative 20 minutes, 4 hours, 24 hours levels, 10 days and 6 months calcium level and 20 minutes, 4 hours and 24 hours PTH level and postoperative complications (temporary and permanent recurrent laryngeal nerve damage, delayed and permanent hypocalcaemia, early bleeding requiring re-operation) and histopathology results of the 85 patients who had total thyroidectomy were recorded. Also the demographical features of the patients, their preoperative and postoperative diagnosis and the operation team were recorded.

Indications for surgery; patients with suspected malignancy or diagnosis after fine needle aspiration biopsy, patients with pressure symptoms and did not benefit from medical treatment or patients with benign multinodular goiter causing cosmetic problems and patients with diffuse or nodular hyperthyroidism. The decision for surgery of the patients was taken by endocrinologists, nuclear medicine specialists and general surgeons as a result of their participation to a council. Preoperative thyroid function tests of all the patients were examined. Fine needle aspiration biopsy, thyroid ultrasonography and thyroid scintigraphy (if needed) were performed. The patients who had hyperthyroidism before the surgery became euthyroid.

Parathyroid hormone was analyzed with Electrochemiluminescence immunoassay method. Venous blood samples were taken and analyzed for postoperative 20 minutes, 4 hours and 24 hours parathormone and calcium levels. Before the patients were discharged, they were examined for chvostek and trousseau findings with physical examination then they were discharged in accordance with their 24th hour PTH levels. According to our laboratory, normal parathormone values are 10-65 pg / mL. Therefore, the patients with < 10 pg/ml parathormone levels were hospitalized one more day and they were discharged after intravenous (IV) calcium replacement, 2-5 g / day of calcium carbonate and 0.5-1 mg / day calcitriol. The patients with 10-20 pg/ml PTH level were discharged only with calcium carbonate. Those with higher than 20 pg/ml PTH level were not given any treatment.

According to our laboratory, normal calcium values are 8.4-10.2 mg/dl. Hypocalcemia was defined as the serum calcium level below 8.4 mg/dl. Hypocalcaemia symptoms were described as numbness in the extremities, tingling and cramps by the patients. Dose adjustment was made depending on the calcium level postoperative second week. The patients were considered to have permanent hypocalcaemia after ongoing hypocalcaemia was observed and venous blood sample was taken and analyzed on the sixth month.

Ethical approval: The authors confirm that this prospective work was performed in compliance

with Ethical Standards and according to Institutional Review Board standards. This prospective work was approved by Akdeniz University Faculty of Medicine Clinical Research Ethics Committee.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Statistic Analysis: Data were analyzed by using SPSS (Statistical Package for Social Sciences) for Windows 18.0 and MedCalc program. PTH levels analyzed in various time intervals in cases of transient hypocalcaemia were analyzed by Whitney U test. Whether PTH and calcium levels show any change in time was analyzed using variance analysis in repeated measurements. Sensitivity of PTH levels analyzed in various time intervals in condition of transient hypocalcaemia was measured using ROC curve. Sex distribution in cases of transient hypocalcaemia was investigated using Chi-square analysis. Results were evaluated at %95 confidence interval and significance was evaluated at $p < 0.05$ level.

RESULTS

The average age of 85 patients who underwent total thyroidectomy was 51.55 (26-71). 15 patients were male (%17.6) and 70 patients were female (%82,4), no significant difference ($p:0,076$) was observed in hypocalcaemia rate of the patients considering their sex. 64 (%75.3) of the patients were operated with prediagnosis of benign thyroid diseases and 21 (%24.7) of them were operated with prediagnosis of malign thyroid diseases. As a result of the histopathological evaluation 63 (%74) patients out of 85 were reported as benign and 22 (%26) of them were reported as malign cases. One patient was detected to have thyroid epithelial malignant tumor metastasis. 2 patients had 2 and the other 2 patients were reported to have 1 parathyroid tissue out of 4 patients (%4.7) in the study group. 14 (%16.5) patients out of 85 who were operated for total thyroidectomy had hypocalcaemia In their 6-month follow-up, 4 patients (%4.7) were reported to develop hypocalcaemia. Permanent hypocalcaemia. 11 (%78.5) of the patients who developed transient hypocalcaemia were diagnosed with benign thyroid disease and 3 (%21.5) of them were diagnosed with malign thyroid disease. 20 minutes, 4 hours and 24 hours

average PTH levels of patients with transient hypocalcaemia were respectively 12,1 pg/ml, 12.6 pg/ml and 14.3 pg/ml, and an increase was observed directly proportional with time. 20 minutes, 4 hours and 24 hours average PTH levels of patients with permanent hypocalcaemia were respectively 7.2 pg/ml, 7.0 pg/ml ve 7.5 pg/ml and an increase was not observed directly proportional with time.

Postoperative 20 minutes, 4 hours and 24 hours PTH levels were statistically significant ($p:0,0001$) in the diagnosis of hypocalcaemia. 20 minute PTH level among PTH levels was statistically more sensitive (%91.5) in specifying postoperative hypocalcaemia (Table 1. The sensitivity and specificity of PTH level over time.). 24 hour PTH level's sensitivity %85.9 and specificity %85.7. In Patients with low PTH levels and normocalcemia in the first 24 hours after surgery, hypocalcemia didn't occur after 24 hours.

The comparison of postoperative calcium level sensitivity in the diagnosis of hypocalcaemia did not yield a significant difference (Table 2. The sensitivity and specificity of calcium level over time.).

3 patients out of 14 who had postoperative hypokalemia had symptoms such as numbness in the extremities, tingling. No patient developed tetani. PTH was found < 10 pg/ml in 3 patients with symptomatic hypocalcaemia.

Recurrent laryngeal nerve injury was not observed in any patient. One patient who had bleeding on the postoperative same-day was explored and hemostasis was achieved. Hypocalcaemia was not observed in the postoperative follow-ups.

Table 1. The sensitivity and specificity of PTH level over time.

	Sensitivity	Specificity
20 minute PTH	%91,5	%100
4 hour PTH	%78,9	%100
24 hour PTH	%85,9	%85,7

Table 2. The sensitivity and specificity of calcium level over time.

	Sensitivity	Specificity
20 minute Ca ⁺⁺	%48.6	%39.8
4 hour Ca ⁺⁺	%49.9	%43.4
24 hour Ca ⁺⁺	%50	%67.5

DISCUSSION

Thyroid gland diseases affect %3-5 of the population and it is the most commonly seen endocrine disease after diabetes mellitus [3]. Main complications of thyroid surgery are inferior and superior laryngeal nerve injury, hypocalcaemia and bleeding [4]. Bleeding and laryngeal nerve injury show themselves in the postoperative early stage (1-8 hours). Hypocalcaemia is examined in two subgroups as permanent and transient hypocalcaemia. Hypocalcaemia recovered up to postoperative 6 month-treatment period is usually accepted as transient. On the other hand, hypocalcaemia which requires exogenous calcium and vitamin D and which has a value under the biochemically accepted level is usually named as permanent hypocalcaemia. Some authors specify this period as 1 year [3].

After thyroid operations, a physiological decrease in the serum calcium level can be observed in 12-24 hours and most of these cases automatically recover in 24 hours. Simultaneously, serum phosphate decreases in a much lesser degree. Hemodilution, renal tubular calcium absorption amount and calcitonin secretion which are caused by antidiuretic hormone released after surgery based stress can lead to these changes [5].

The most important cause of hypocalcaemia developed after thyroidectomy is hypoparathyroidism [6]. Hypoparathyroidism develops after trauma of the parathyroid glands, parathyroid devascularization, and accidental removal of the parathyroid tissue located at the top or rarely at the bottom of the thyroid capsule. Also in thyrotoxic patients, factors such as hungry bone syndrome and hemodilution are responsible for the development of hypoparathyroidism [7].

Incidental parathyroidectomy during thyroidectomy is observed %8-19 in literature, however correlation of extracted parathyroid glands with symptomatic hypocalcaemia is not observed [8]. If at least one parathyroid gland maintains its vitality, no permanent hypocalcaemia is expected unless deterioration takes place in calcium absorption of gastrointestinal system [9]. In our study incidental parathyroidectomy rate was found to lower than literature but still the rate is %4.7. Among these 4 cases, 2 of them developed transient hypocalcaemia and 1 developed permanent hypocalcaemia.

The cause of permanent hypocalcaemia was interpreted as parathyroid ischemia.

Hypocalcaemia may not yield any symptoms in the first 48 hours. Hypocalcaemia which shows itself as paresthesias, carpopedal muscle spasms, anxiety in patients is transient and recovers automatically, but if the parathyroid glands are damaged irreversibly it may become permanent [10]. In case of permanent hypocalcaemia, patients need lifetime medication and also it affects patients' quality of life in a negative way. In a retrospective study, transient hypocalcaemia was detected to be %19,9, permanent hypocalcaemia was %3,8 [11]. In our study, transient hypocalcaemia rate was %16,5 and permanent hypocalcaemia rate was %4,7, our rates are similar to that of the literature.

Hospitalization of the patients for 48-96 hours because of the hypocalcaemia that may develop postoperative 48-72 hours is a common method in many hospitals [12]. This circumstance increases the cost of surgery and affects the social lives of patients negatively. An effective parameter analyzed in an early postoperative stage for patients who underwent total thyroidectomy may enable patients to be discharged safely 24 hours later at the latest. Fast parathormone measurement has been a commonly used method for the past 10 years in parathyroid and thyroid surgery [13].

In a retrospective study, PTH was analyzed in the 4th hour after total thyroidectomy for 271 patients forming the first group of the study and for 100 patients forming the second group, calcium was analyzed on the postoperative first day. 0.5 µg/day calcitriol and 2-6 gr/day calcium carbonate was prescribed at the time of discharge on the first day for patients with PTH level lower than (10-72 pg/ml) 10 pg/ml. Only calcium carbonate was prescribed for those who had PTH level of 10 pg/ml and higher. Calcium carbonate was prescribed for the second group patients depending on the surgeon. 19 patients (%7) of the first group and 17 patients (%17) of the second group developed symptomatic hypocalcaemia. It was statistically found significant ($p:0.005$) for the first group of patients to develop less hypocalcaemia. In the study, 5 patients (%1.8) of the first group and 8 patients (%8) of the second group applied to the

emergency service with symptoms of hypocalcaemia. Oral calcium and calcitriol treatment together with intravenous calcium infusion was given to the patients. This practice brings an extra burden in terms of the cost of treatment. Thus, only PTH measurement itself lowers the rate of emergency service application of the patients with symptoms of hypocalcaemia. This method is a cheap and easy to follow treatment protocol [14].

In our study 3 patients who developed symptomatic hypocalcaemia applied to the emergency service with complaints of numbness in the extremities and tingling. 2 of these patients were prescribed calcium carbonate at the time of discharge and the other patient was not prescribed calcium carbonate since the patient's calcium level was normal. These patients were given IV calcium infusion. No patient developed tetani. These 3 patients with symptomatic hypocalcaemia had a level of PTH < 10 pg/ml.

In our study, PTH levels analyzed on the postoperative 20 minutes, 4 hours and 24 hours were found to be statistically significant ($p:0,0001$) to be able to detect hypocalcaemia in an early stage. But PTH level was found to be statistically more sensitive (%91.5) on the postoperative 20 minutes. In a prospective study, there was no statistically significant difference ($p>0.05$) between postoperative PTH level analyzed in the recovery room and postoperative 24th hour PTH level [15]. In a similarly conducted study, PTH level in the blood taken during the closure of the skin was %80 sensitive and %100 specific in predicting hypocalcaemia [16]. In another prospective study on PTH and calcium levels of the patients who underwent thyroidectomy, postoperative 1st hour PTH level was found to be %100 sensitive for hypocalcaemia [17].

In the literature, there are studies indicating that postoperative calcium levels must be taken into consideration and studies reporting that patients must be discharged in accordance with their postoperative or intraoperative PTH levels to be protected from probable hypocalcaemia that may develop after total thyroidectomy. It was reported that patients can be discharged safely according to their calcium levels analyzed in the postoperative early stage [18,19]. In our study also serum

calcium level was found >8 mg/dl in 2 out of 4 symptomatic patients on the first postoperative morning. In our study, no statistically significant difference was found when the sensitivity of calcium levels were compared in accordance with time.

As a conclusion; calcium monitorization surely has an important place in endocrine surgery for the diagnosis of symptomatic hypocalcaemia. It is a well-known fact that this method is more economical compared to parathormone measurement. Absence of a safe, effective and economical parameter for early discharge of patients and quality control in thyroid surgery is strongly felt. Therefore, follow-up with PTH measurement is more effective than follow-up with calcium measurement according to our study. The frequency of hypocalcaemia based findings, duration of patients' hospitalization and the number of applications to the emergency service is lowered with this method. Moreover, this method is more economical and easier with follow-up than routine calcium and/or vitamin D replacement. We are in the opinion that with a PTH level analyzed on the 20th postoperative minute, patients can be discharged safely 24 hours after the surgery and we also believe that in the presence of a higher than 10 pg/ml PTH level we will not observe postoperative hypocalcaemia symptoms.

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